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Research Article

Cerebral Microinfarcts Are Common in Undiagnosed Lung Cancer Patients: A Population-Based Study

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Background. Cerebral microinfarcts (CMI) represent covert brain ischemia and were associated with stroke risk and cognitive impairment. Magnetic resonance imaging diffusion-weighted imaging (DWI) hyperintensities have been suggested to represent acute CMI. The relationship between malignancy and CMI is unknown. *Aims*. We aimed to examine whether CMI is more common in patients with undiagnosed lung cancer, and therefore might serve as a prediction marker for cognitive impairment or cancer-related stroke. *Methods*. We used the computerized database of Clalit Health Services (the largest healthcare provider in Israel) to identify adults diagnosed with lung cancer who had an MRI brain scan for any indication prior to cancer diagnosis. We analyzed DWI sequences, in order to evaluate CMI incidence in this population, and compared it to control groups of patients with other undiagnosed malignancies and patients without known cancer. *Results*. Altogether, we reviewed 1822 MRI brain scans, of which 497 scans were taken in patients with undiagnosed lung cancer, 543 scans of noncancer patients, and 793 scans of patients with other undiagnosed malignancies. In the lung cancer group, we found 24 CMI, compared with 4 in the noncancer group ($p = 0.04$) and 8 in the other cancer group ($p = 0.07$). *Conclusions*. CMI is common in undiagnosed lung cancer patients compare to other undiagnosed cancer types or noncancer patients. At the time of lung cancer diagnosis patients may be at risk for future stroke or cognitive decline.

1. Introduction

Cerebral microinfarcts (CMI) are probably the most common type of brain infract [1, 2]. Due to their microscopic size, they are undetectable on gross pathological examination or conventional structural magnetic resonance imaging (MRI) sequencing. CMI can be detected, however, as hyperintense signals on MRI diffusion-weighted imaging (DWI) only for a period of 5-14 days [3].

A randomly detected small DWI lesion on brain MRI implies the annual incidence of hundreds of new microinfarcts [4]. These CMI play an important role in cognitive decline [5] and are associated with symptomatic lacunar strokes [2].

CMI is only one of the features of cerebral small vessel disease (CSVD) [6], a clinical, neuroimaging, and neuropathological syndrome of brain small perforating arterioles, commonly associated with cardiovascular risk factors and atherosclerosis [7].

Arterial and venous thrombosis is a well-known complication of lung cancer [8–11]. A recent study has shown that arterial thromboembolic events can precede cancer diagnosis, especially lung and colorectal cancer, even 5 months before cancer was formally diagnosed, with peak relative risk in the month prior to cancer diagnosis [12].

To the best of our knowledge, no study has ever looked at the association between ongoing silent brain ischemia and undiagnosed lung cancer.

We aim to determine whether populations with undiagnosed lung cancer show a higher rate of DWI hyperintense lesions, as a sign of ongoing silent cerebral microinfarction, compared with patients with other types of malignancy and patients without diagnosis of malignancy.

2. Methods

2.1. Setting and Data Source. This is a retrospective cross-sectional study of the Clalit Health Services (CHS) database. CHS is the largest of the four health maintenance organizations in Israel. The comprehensive CHS electronic data system receives and aggregates continuous real-time inputs from its physicians and health services providers, including medical diagnoses, lab results, and imaging acquisitions of both inpatients (14 CHS hospitals in Israel) and community care. CHS has approximately 4.7 million members representing over half of the Israeli population. Accordingly, the CHS database has a sample representative of the Israeli population.

Our collaboration group, prediction analysis for intracerebral hemorrhage (PREACHER), retrospectively investigate CSVD imaging markers, among other clinical outcomes and comorbidities, using individual patient data. The main aim of our group is to achieve large-scale analysis of thousands of brain MRI scans, searching for correlations between CSVD markers and clinical outcomes. For this specific research, data has been derived from the electronic database of CHS regarding the diagnosis of cancer and the acquisition of brain MRI.

We included patients who had a diagnosis of either a lung (ICD-9 162), pancreas (ICD-9 157), colorectal (ICD-9 153), or breast carcinoma (ICD-9 174-175), between January 2014 and April 2020, and had brain MRI for any indication at any time prior to cancer diagnosis. We excluded patients without DWI sequences or evidence of metastases on the MRI scan. We had 3 groups: undiagnosed lung cancer (lung cancer group), undiagnosed patients with other malignancies (nonlung cancer control group - NLCCG), and an aged-match noncancer control group (NCCG).

2.2. Ethics Approval and Consent to Participate. The study was approved by the Carmel Medical Center Ethics Committee (study number 0041-17-CMC), combined with the approval of the Central Data-Extraction Committee of CHS. The need for informed consent was exempted by the Carmel Medical Center ethics committee (IRB 0041-17-CMC) as this is a retrospective population-based cohort study.

2.3. Imaging Reading. CMI was defined as hyperintense lesions on DWI, smaller than 2 cm, with an apparent diffusion coefficient (ADC) hypointense correlate in its exact location, and without hypointense susceptibility weighted imaging (SWI) correlate in that location. Due to the blooming effect, the real lesion size is much smaller than it appears in imagining. Lacunes were defined as hypointense lesions between 3 mm and about 15 mm in diameter usually with hyperintense rim, on fluid-attenuated inversion recovery (FLAIR) sequence; white matter hyperintensities (WMH) were defined as a signal abnormality of variable size in the white matter, hyperintensity in FLAIR without cavitation. We rated WMH with a Fazekas score from 0-3 [13]. Cerebral microbleed (CMB) was defined as small (<10 mm) areas of a signal void with associated blooming in SWI or gradient echo sequences (GRE) [6].

The MRI scans were reviewed by a group of neurologists, radiologists, and medical student. All participants underwent teaching and practical training in reading imaging by an experienced neuroradiologist (R.E.) and an experienced vascular neurologist (E.A).

Interrater reliability was calculated with intraclass correlation coefficients (ICCs) from two-way ANOVA analysis that were derived to compare all readers. The results were 0.8 (95% CI, 0.76-0.85) for CMI, 0.92 (0.87-0.96) for WMH, 0.79 (0.69-0.88) for lacunes, and 0.81 (0.76-0.85) for microbleeds. Higher values represent a better agreement between the readers, and all ICCs were either good (≥ 0.75) or excellent (≥ 0.9) [14].

FLAIR, ADC, and SWI sequences were also evaluated to exclude other non-CMI lesions, such as CMB or metastases [15]. When available, MRI reports and indications were reviewed to exclude symptomatic CMI (i.e., acute neurological signs such as hemiparesis, hemihypesthesia, or dysphasia).

We also looked at other CSVD markers: WMH, lacunes, and CMB. We only looked at the first FLAIR, SWI, or GRE sequence for each patient, even if a patient had multiple MRI scans.

As mentioned, CMI is detectable only for a short period. For this reason, the probability of detecting CMI depends on the time window. Former studies used the annual incidence of CMI to estimate to total burden of CMI in a certain population: this can be calculated by the total number of CMI found in all MRI scans, multiple by the number of windows per year (for example, 365/10 if we assume that each lesion stays for 10 days [3, 4, 16]), and divided by total MRI scans [17].

2.4. Statistical Analysis. Numerical variables were described using frequency and percentage, and ANOVA was used for comparison for normal. Categorical variables were described using frequency and percentage, and Pearson's chi-square test or Fisher's exact test was used to compare categorical

variables. Multinomial logistic regression was used for significant data. Nonparametric tests Mann–Whitney *U* Test and Kruskal-Wallis H Test were chosen for analyses of a number of CMI and CMB because of skewed distributions. We modeled the binary option of positive versus negative DWI using binary logistic regression with generalized estimating equations to handle the dependence in the data.

For calculating annual CMI risk, assuming the lesion detectable for 10 day [3], annual prevalence would be calculated as $(365/10) \times (\text{CMI number/total MRI scans})$ [18]. A p value < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY).

3. Results

Our cohort had 1348 patients with 1822 MRI scans. The lung cancer group contained 384 with 486 MRI brain scans, the mean age was 68 years, and 42% of patients were females. Patients underwent brain MRI in the 6 years prior to cancer diagnosis (median 175 days (30,634)). NLCCG contained 586 patients with 793 MRI scans with a mean age of 64, patients underwent MRI in the 6 years prior to cancer diagnosis (median 620 (254, 1059)). NCCG contained 378 patients with 543 MRI scans, and demographic and cardiovascular risk factors at the time of MRI are described in Table 1. The lung cancer group and NLCCG had a higher prevalence of diabetes, myocardial infarction, and obesity than the NCCG. There was a higher prevalence of smoking in the lung cancer group.

There was a total of 24 CMI (see Figure 1) in the lung cancer group compared to four in NCCG ($p = 0.043$), and eight in NLCCG ($p = 0.07$). p value for multigroup comparison was 0.068. In the lung cancer group, 11 patients)2.2%) had CMI, compared to 4 patients in the NCCG (0.7%, $p = 0.056$) and 8 in the NLCCG (1%, $p = 0.09$). p value for multigroup comparison was 0.07 (Table 2).

In a subanalysis of the occult phase of lung cancer (2 years prior to diagnosis), we found a total of 14 CMI in 7 patients out of 327 lung cancer patients (p value of 0.068 and 0.071, respectively, compared with noncancer patients).

Assuming the lesion stays positive for 10 days, the calculated annual risk was 1.8 CMI incidence per year in lung cancer patients [18]. In the NLCCG, the calculated risk was 0.36 per year, and in the NCCG, the calculated incidence was 0.27 per year.

There was no statistically significant difference between CMI-positive and CMI-negative patients in demographic and clinical characteristics (Table 3). Other CSVD changes, such as lacunes, WMH score, and CMB were examined as well, with more lacunes and CMB in the CMI-positive group (Table 3). After performing logistic regression, CMI-positive patients tend to have more CMB ($p = 0.038$).

4. Discussion

We found that patients with lung cancer have significantly more CMI than noncancer patients, indicating silent active brain ischemia. We also found a trend towards more CMI in lung cancer patients compared to NLCCG. Moreover, the calculated annual incidence of CMI [19] is approximately fivefold higher in lung cancer patients than in the NLCCG as well as NCCG. None of the other risk factors was found to be associated with CMI.

It should be noted that the real CMI incidence is likely to be even higher, as MRI resolution in clinical practice can only detect lesions larger than several millimeters, and even ultrahigh field strength MRI imaging can detect only CMI larger than 1-2 mm [20], while smaller lesions can be detected only using microscopic histopathology [21].

It is well established from clinic-pathological studies that cortical CMI promotes dementia and cognitive decline [1, 22]. Therefore, our results may imply that patients with undiagnosed lung cancer might be at risk for cognitive impairment secondary to CMI. This question deserves a future prospective study, looking at cognitive performances in lung cancer patients.

Cancer-associated stroke is an emerging entity [23–26], attributed mainly to hypercoagulability and thromboembolism in mucin-producing adenocarcinomas such as pancreatic, gastrointestinal tract, lung, and ovarian cancers [10, 27]. Patients with cancer, however, do not routinely are being treated with antithrombotic [28, 29]. A previous study showed that lung cancer is the most common malignancy associated with stroke with a cumulative incidence of ischemic stroke of 6.9 in the first year, compared with 3.2 in the control group [10]. This reinforces the question of whether preventive antithrombotic therapy should be administrated in this population. Prior study has shown that the relative risk for cancer 6 months after arterial thromboembolism is highest in patients without selected CV risk factors [30], and thrombosis might indicate occult lung cancer [23]. However, no previous studies looked at silent brain ischemia. Therefore, our results also suggest that in patients with incidental CMI, and no other explanation, such as ipsilateral carotid stenosis or atrial fibrillation, lung imaging should be considered.

A total of 2.2% of patients with undiagnosed lung cancer in our cohort were found to have CMI indicating that CMI is more prevalent relative to the general population or even to subjects with vascular risk factors or cognitive decline. In a population-based study of 793 participants from Canada, no incidental DWI lesions were found [31]. A study of 16,206 patients found that the prevalence of CMI was only 0.37% [32]. In a population with vascular risk factors, the prevalence was 1% [19]. A cohort of 649 patients with memory impairment reported a prevalence of 0.9% [33].

The main strengths of our study are the large cohort size and the comparable control groups, as other studies looking at CMI incidence in other populations had no control groups [19, 31, 33]. Some limitations should be considered: First, this is a retrospective cross-sectional study. Second, there were some differences in the prevalence of cardiovascular risk factors including smoking. However, diabetes and myocardial infarction were more common in the NLCCG and the lung cancer group compared with the NCCG. Moreover, there were no differences in cardiovascular risk factors between patients with positive CMI and

Table 1: Comparison between other cancer group, lung cancer group, and noncancerous group.

	Noncancer control group, *n* (%) *n* = 378	Nonlung cancer control group, *n* (%) *n* = 586	Lung cancer, *n* (%) *n* = 384	*p* value
Demographic data				
Age (mean ± SD)	65.5 ± 11.9	64.1 ± 12.5	68 ± 9.5	<0.01
Gender (female)	236 (62%)	437 (75%)	160 (42%)	<0.01
Comorbidities				
Congestive heart failure	10 (3%)	32 (5%)	10 (3%)	0.11
Hypertension	187 (49%)	279 (48%)	205 (53%)	0.08
Diabetes mellitus	84 (22%)	171 (29%)	113 (29%)	0.02
Stroke	6 (2%)	11 (2%)	8 (2%)	0.88
Atrial fibrillation	19 (5%)	47 (8%)	33 (8%)	0.06
Myocardial infarction	26 (7%)	55 (9%)	55 (14%)	<0.01
Obesity	100 (26%)	207 (35%)	117 (30%)	0.02
Smoking (past or current)	125 (33%)	229 (40%)	302 (78%)	<0.01
Carotid artery disease	10 (3%)	23 (4%)	23 (6%)	0.07
Aortic aneurysm	3 (1%)	7 (1%)	9 (2%)	0.16

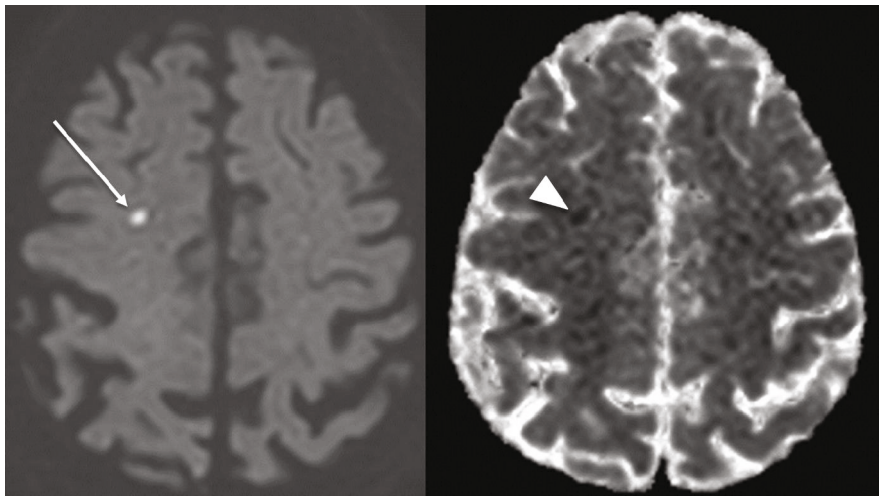

Figure 1: Right frontal hyperintense signal on the diffusion-weighted imaging sequence (white arrow). Corresponding hypointensity is shown on the apparent diffusion coefficient sequence (arrowhead) suggesting cerebral microinfarct.

Table 2: Comparison between noncancer, lung cancer, and other cancer groups for positive CMI* in DWI** scans and total CMI in MRI scans.

	Lung cancer vs. NCCG***	Lung cancer vs. NLCCG****	NCCG vs. NLCCG	*p* value between 3 groups
Total CMI in each group (*n*)	24 vs. 4	24 vs. 8	4 vs. 8	
p value	0.043	0.077	0.077	0.068
CMI incidences MRI with CMI lesion/total MRI scans, %	11/486, 2.2% vs. 4/543, 0.7%	11/486, 2.2% vs. 8/793, 1%	4/543, 0.7% vs. 8/793, 1%	
p value	0.056	0.09	0.77	0.07

*CMI: cerebral microinfarcts; **DWI: diffusion weighted imaging in MRI; ***noncancer control group; ****nonlung cancer control group.

negative CMI (Table 3). Third, some patients had MRIs up to 6 years prior to diagnosis. A positive trend, however, was found also in a subanalysis looking at the occult phase only (2 years prior to diagnosis). Fourth, several readers with different training and experience participated in the study, interrater reliability, however, was found to be high. Fifth,

Table 3: Comparison between positive CMI* in DWI** to negative DWI scans for CMI in all cohorts.

	Positive CMI patients, n (%) $n = 22$	Negative CMI patients, n (%) $n = 1326$	p value	p value for binary logical regression
Demographic data				
Age (mean ± SD)	68.7 ± 8.3	65.5 ± 11.7	0.09	—
Gender, female	10 (45%)	823 (62%)	0.08	—
Comorbidities				
Hypertension	15 (68%)	656 (50%)	0.56	—
Diabetes mellitus	10 (45%)	358 (27%)	0.13	—
Atrial fibrillation	4 (18%)	95 (7%)	0.11	—
Congestive heart failure	0	52 (4%)	0.62	—
Myocardial infarction	7 (32%)	129 (10%)	<0.01	0.25
Stroke	0	25 (2%)	1	—
Smoking	15 (68%)	641 (48%)	0.17	—
Chronic obstructive pulmonary disease	2 (9%)	145 (11%)	1	—
Carotid artery disease	2 (9%)	54 (4%)	0.23	—
Aortic aneurysm	1 (5%)	18 (1%)	0.27	—
Other CSVD*** features				
Cerebral microbleeds (mean ± SD)	4.9 ± 16.9	0.8 ± 2.8	<0.01	0.038
Lacunes (mean ± SD)	1.1 ± 2.5	0.6 ± 1.7	0.02	0.37
White matter hyperintensities				
0	2 (9%)	393 (30%)	0.08	0.47
1	9 (41%)	571 (43%)		
2	5 (23%)	218 (16%)		
3	6 (27%)	144 (11%)		

*CMI: cerebral microinfarcts; **DWI: diffusion weighted imaging in MRI; ***CSVD: cerebral small vessel disease.

just like most MRI-based retrospective studies, different protocols, scans, and MRI machines were used. Sixth, we did not have a pathological correlation with DWI lesions to confirm CMI presence, but a previous study approved the correlation [16]. Seventh, as this is a retrospective cross-sectional study, and patients underwent a scan for multiple indications prior to cancer diagnosis; we did not have sufficient data about D-dimer. And lastly, although CMI is defined as nonsymptomatic lesions, we did not have access to clinical indications for imaging; therefore, it is possible that some of the lesions were symptomatic. The latter is unlikely, due to lesions' small size.

5. Conclusions

We showed that CMI is not uncommon in the undiagnosed phase of lung cancer patients, in contrast to NLCCG or NCCG, demonstrating the thrombotic effect of latent lung cancer on CSVD. Our findings may imply that at the time of cancer diagnosis lung cancer patients may be at risk for cognitive decline or future stroke. This might suggest that antithrombotic therapy should be considered as primary stroke prevention in patients following lung cancer diagnosis and incidental CMI. Implementing this approach in lung cancer patients with CMI is crucial, as these patients undergo brain MRI annually as a part of the routine workup, as opposed to NLCCG. Moreover, incidental CMI on MRI might suggest the need for lung cancer screening. Future studies should also investigate the emerging question of occult brain ischemia after lung cancer is diagnosed.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

The study was approved by the Carmel Medical Center Ethics Committee (study number 0041-17-CMC), combined with the approval of the Central Data-Extraction Committee of Clalit Health Services. All procedures were carried out in accordance with relevant guidelines and regulations. Since this was not an interventional study, obtaining informed consent was exempt.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Jonathan Naftali M. D. performed the study design, data collection, data analysis, and writing of the paper. Rani Barnea

M.D. did the study design and data collection and provided a critical review of the manuscript. Ruth Eliyahu M.D. worked on the data collection. Assaf Tolkovsky M.D. executed the data collection. Keshet Prado M.D. worked on the data collection. Michal Zukerman M. D. did the data collection. Noa Soback worked on the data collection. Meital Adi M.D. worked on the data collection. Avi Leader M. D. provided a critical review of the manuscript. Sivan Bloch M.D. provided a critical review of the manuscript. Walid Saliba MD, MPH worked on the data analysis and provided a critical review of the manuscript. Eitan Auriel M.D., MSc accomplished the study design, data analysis, and provided a critical review of the manuscript.

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